NANOMATERIAL-BASED ELECTROCHEMICAL SENSING OF SOME ORGANIC COMPOUNDS WITH MEDICINAL PROPERTIES

A
SYNOPSIS
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ORIGIN OF THE PROBLEM

The development of pharmaceutical drugs has brought a revolution in human health. Guided by pharmacology and clinical sciences, and driven by chemistry, pharmaceutical research in the past has played a crucial role in the progress of development of pharmaceuticals. These pharmaceuticals would serve their purpose only when they are free from impurities and administered in appropriate amount. Thus, detection and quantification of these pharmaceutical drugs is necessary to ensure adequate drug level and understand the redox mechanism which gives an idea of in-vivo fate of drug as it is assumed that redox mechanism of the drug at the electrode surface and in the body share the similar principle.

The techniques such as HPLC, LC/MS, spectrophotometry and microbiological assay are used for drug determination in pharmaceutical formulation and biological fluids, but these are expensive and time consuming techniques which involve heavy instrumentation and sample pretreatment. Whilst, electrochemical techniques are highly sensitive, selective, simple, rapid and low cost analytical methods which make them suitable for routine analysis.

A detailed survey of literature has revealed the wide applicability of electrochemical analysis of pharmaceutical drugs yet there are some pharmaceutical drugs which need to be explored by this technique.

The purpose of the present research work is to combine the advantages of nanomaterials based sensors and voltammetry for sensitive and selective determination of the pharmaceutical drugs. It is intended to achieve lower limits of detection and quantification with a stable sensor. The optimization of the parameters such as effect of pH, variation in potential and scan rate, nature of surfactants and stability using Cyclic, Square wave and Differential pulse voltammetry will be carried out mainly focusing on modification of electrode. Method validation in terms of accuracy, precision, specificity and selectivity will be carried out. This work is focused mainly on the fabrication of a sensitive sensor for monitoring of some organic compounds with medicinal properties.

ABBREVIATIONS

DME- Dropping Mercury Electrode

mCPE- Modified Carbon Paste Electrode

GCE- Glassy Carbon Electrode

HMDE-Hanging Mercury Drop Electrode

MIP-Molecularly Imprinted Polymer

GR-Graphene

BDDE-Boron Doped Diamond Electrode

MWCNT- Multi-Walled Carbon Nano Tube

p-tol – Para Toluene

ILs- Ionic Liquids

CV- Cyclic Voltammetry

DPV- Differential Pulse Voltammetry

SWV- Square Wave Voltammetry

DPP- Differential Pulse Polarography

AAdSV- Anodic Adsorptive Stripping Voltammetry

SWAdSV- Square Wave Adsorptive Stripping Voltammetry

DPAdSV- Differential Pulse Adsorptive Stripping Voltammetry

SWCAdSV- Square Wave Cathodic Adsorptive Stripping Voltammetry

INTRODUCTION

Electroanalytical chemistry is a sub-division of analytical chemistry that engages electrochemical methods to retrieve information related to the amounts, properties, and environments of chemical species. Isaac Maurits Kolthoff once defined electroanalytical chemistry as the application of electrochemistry to analytical chemistry. It is desirable to visualize electroanalytical chemistry as that area of analytical chemistry and electrochemistry which uses electrode as a probe, to measure something that directly or indirectly involves the electrode (Plambeck 1982). The best known analytical techniques are the electrochemical methods which possess the following advantages: easy instrumentation, moderate cost and portability, high speed, high scan rates, accuracy, and precision, large linear dynamic range with no pollution effect and insignificant effect of the matrix from endogenous substances in biological media or from excipients in pharmaceutical dosage forms (Kauffmann and Vire, 1993; Jain et al. 1997; Torres et al. 2002; Abdine and Belal, 2002; Santos et al. 2005; Jain et al. 2006; Silva et al. 2006; Sun and Zhang, 2007; Farghaly et al. 2014).

Electroanalytical methods such as linear sweep, cyclic, differential pulse, square wave, stripping voltammetric techniques and chronoamperometry are capable of determining amounts of an electroactive compound as well as useful information regarding its physical and chemical properties (Smyth and Vos, 1992; Kissenger and Heineman, 1996).

One of the most important branches of applied analytical chemistry is pharmaceutical and biomedical analysis. The escalation in the demand of pharmaceuticals calls for higher level of quality control. There are chances that these pharmaceuticals may develop impurities at various processing stages, thus making them risky for administration. Therefore, development of a new analytical method seems appropriate for quantitative and qualitative investigation of bulk drug materials, the intermediates, drug impurities, biological samples containing drugs and their metabolites (Siddiqui et al. 2013; Bozal et al. 2011). Moreover, the newly developed drugs with high physiological activity are administered in smaller

amounts, thus indicating the need for the development of a highly sensitive and selective analytical method (Patriarche and Zhang, 1990).

In such cases, modern electroanalytical methods can be viable alternative to more frequently used spectrometric or separation methods which pose certain disadvantage such as high costs, long analysis time, complex and tedious sample pretreatment and in some cases low sensitivity and selectivity which makes them less suitable for routine analysis (Sarre et al. 1992; Kang et al. 1997; Guan et al. 2000).

The knowledge of an electrode process of drug compounds provides a useful aid for understanding of its enzymatic processes and oxidation/reduction mechanisms after administration in the body. The characteristics of electroanalytical techniques make the analysis, of these trace amount of drugs, particularly well suited for automatic in situ speciation measurements, with or without minimum sample change. The quantization of trace and ultra-trace components in complex samples of clinical or industrial origin represents an important task of modern electroanalytical chemistry (Zhang et al. 2008).

One of the widely used electroanalytical techniques is voltammetry, which is a current-voltage technique where the applied potential is continuously varied at the electrode-solution interface and the resulting current is measured. Several examples in the literature report the existence of relationship between the voltammetry and pharmacological activity of the drugs (Kauffmann et al. 1985; Dakova et al. 1990; Kovacic et al. 1989; Ames 1991) and the knowledge of their mechanism helps us to understand the mechanism of interaction of drug with living cells (Ozkan et al. 2003; Kounaves, 1997).

The development of chemical and biological sensors is currently one of the most active areas of analytical research. Sensors are small devices that incorporate a recognition element with a signal transducer. Such devices can be used for direct measurement of the analyte in the sample matrix (Zhang et al. 2008). It has been demonstrated that the use of solid electrodes depicts the most rapidly growing class of sensors. Moreover, the beauty of electrochemical techniques is to utilize chemically modified electrodes (CME) tailor made, for refined sensitivity and selectivity for determination of the active compounds. One of the

distinctive features of CME is that it enhances the electrocatalytic activity and reduces the over potential (Zen et al. 2003).

Remarkable achievements in the field of nanotechnology and nanoscience have paved the way for improved sensitivity and selectivity of electrochemical sensors based on nanomaterials. Undoubtedly, electrode material plays a crucial role in the construction of a high-performance electrochemical sensing device. Additionally, functional nanomaterials produce synergistic effects among catalytic activity, conductivity and biocompatibility to speed up signal transduction as well as amplify the recognition events leading to highly sensitive and selective sensing approach (Zhu et al. 2015).

Attachment of nanoparticles based materials to the electrode surface results in expansion of the true electrode surface area, proper attachment of macro, supra and biomolecules is achieved, electrochemical processes become faster, current signal is enhanced with better resolution of peaks (in case of multiple analytes). The possibility of having different kinds of shapes, of nanocrystallites, and many faces at a particular crystallite, the spatial freedom and orientation of the molecules attached to the nanocrystals is increased. Nanomaterials with catalytic activity are required in lesser amounts thus reducing the cost of electrode.

Different types of substances and materials like metals/ metal oxides and alloys, carbon nanotubes and graphene, inorganic substance polymers and nanocomposites have been employed for surface modification (Donten and Stojek, 2012). Thus, modified electrochemical sensors have become an accepted part of analytical chemistry for they satisfy the emerging need of a simple, rapid and economic method for detection and determination of various analytes including pharmaceutical compounds (Stradiotto et al. 2003).

PRESENT STATE OF KNOWLEDGE

Nanomaterials in Electrochemical Sensors

In recent electrochemical sensing research, nanomaterials have been of great interest due to their electrical conductivity, unique structural and catalytic properties, high loading of biocatalysts, good stability and excellent penetrability (Wang et al. 2008). Many kinds of nanoparticles like metal, oxide and semiconductor nanoparticles have been used for assembling electrochemical sensors and biosensors, and these nanoparticles play different roles in different sensing systems. The important functions imparted by nanoparticles include the immobilization of biomolecules, the catalysis of electrochemical reactions, and enhancement of electron transfer between electrode surfaces and proteins, labeling of biomolecules and even acting as reactant (Luo et al. 2006).

- ***Metal/Metal oxide nanoparticles***

With regard to the electrode material, metal, metal oxides and their hybrid nanocomposites are considered to be the most promising materials (Zhu et al. 2015). The most commonly used metal nanoparticles are of Gold, Silver, Platinum, Palladium and Iridium. Gold and platinum are the most commonly employed nanoparticles for enhancing the rate of oxidation reactions. Ohsaka and coworkers developed an electro-chemical sensor for selective detection of dopamine in the presence of ascorbic acid which resulted in the decrease in the oxidation over potential of ascorbic acid and effective separation of oxidation potentials of ascorbic acid and dopamine thus leading to selective detection of dopamine (Raj et al. 2003). Some of the non-metal nanoparticles such as oxide nanoparticles that have special catalytic properties can also be applied in electrochemical analysis systems. For example, a carbon paste electrode (CPE) doped with copper oxide nanoparticles was developed for the detection of amikacin (Xu et al. 2003). The oxidation current of amikacin at the prepared electrode was about 40 times higher than that at a bulk copper oxide modified CPE.

There have been recent reports on the use of bimetallic nanoparticles. The incorporation of a second metal nanoparticles into a catalytic structure gives opportunities for catalytic fine-tuning, resulting from complimentary and synergistic effects of bimetallic nanoparticles (Rick et al. 2016). Cao and coworkers synthesized bimetallic PtCu nanochains and demonstrated that the sensitivity and specificity was high for glucose detection due to wiring of dispersed crystals, porous nanostructure, clean surface and synergistic electronic effects of the alloyed atoms (Cao et al.2013).

- ***Carbon Nano-structured materials***

Carbon based nano structured materials have been employed extensively in electrochemical sensors. The carbon nanostructures alone as modifier are very active due to their developed surface and specific structure. The application of carbon nanotubes has led to better resolution of the peaks and resulted in lower detection limits in electroanalysis using voltammetry (Chen et al. 2010; Li et al. 2012; Zhou et al. 2011). Recently graphene has become popular for surface modification of electrodes. Graphene holds as a promising electrode material due to its excellent electrochemical properties. Several electrochemical sensors based on graphene and its composites have been developed. In comparison with carbon nanotubes, graphene exhibits potential advantages of low cost, high surface area, ease of processing and safety (Luo et al. 2006).

- ***Conducting Polymers***

Nanodimensional conducting polymers have emerged as another class of potentially beneficial material for electrochemical sensor and biosensor platforms. As with metallic nanoparticles, conducting polymer (CP) nanoparticles have shown to exhibit unique properties like greater conductivity and more rapid electrochemical switching speeds (Innice and Wallace, 2002).

- ***Nanocomposites***

The mixing of nanoparticles and various other materials in appropriate combination offers an improvement for the electrochemical processes. When compared to conventional materials, the properties of nanocomposites can unveil interactive improvements over those of the individual parent constituents.

Nanocomposites have higher surface to volume ratio than the reinforcing material which results in its enhanced mechanical properties, barrier properties, thermal properties and flame retardant properties (Okpala 2014). It is well known that electrode material plays a crucial role in the construction of high-performance electrochemical sensing platforms for detecting target molecules by various analytical methods. Functional nanomaterials can produce synergistic effects among the catalytic activity, conductivity and biocompatibility to accelerate signal transduction (Zhu et al. 2015). Nanocomposites lead to generation of many exciting materials with new properties. The combining properties from the parent material into a single material lead to the possibility that new properties are revealed which were unknown in the parent constituent materials. Thus, nanocomposites find application in many fields including sensors (Okpala 2014). Mostly, conducting polymer/graphene has excellent electrical conductivity. Gao and coworkers developed overoxidized polypyrrole/graphene deposited onto GCE for quantitative detection of adenine and guanine. The sensor showed improved sensitivity and selectivity with low background currents (Gao et al. 2014).

Electroanalytical Methods

It is assumed that the biological reactions happening in the body and the electrochemical reactions occurring on the electrode surface are based on similar principles. The understanding about the redox properties of drugs can give us insight about its in vivo mechanisms. Hence, pharmaceutical drugs can be determined electrochemically with voltammetry (Gupta et al. 2011).

Voltammetry is a class of electroanalytical techniques which is used to assign the current voltage measurement at a given electrode. Polarography is a special case of voltammetry where DME is used for current-voltage measurements (Heyrovsky 1922). Another important branch of voltammetry is stripping analysis which makes it possible to determine trace concentration of the analyte upto sub-nanogram and picogram levels (Ellis and West, 1975; Nickelby and Kooke, 1957; Mars and Shain, 1957; Fargahly et al. 2014; Topal et al. 2010).

Cyclic Voltammetry is mostly the first experiment performed in electrochemical study of drugs in raw materials and pharmaceuticals (Tapsoba et al. 2005; Uslu et al. 2001). It is perhaps the most multifaceted electroanalytical technique in pharmaceutical analysis (Guo et al. 2004; Acuna et al. 2002) which gives us redox behavior of the analyte over a wide potential range. Square Wave Voltammetry is another achievement in the field of electroanalytical chemistry with high speed with an effective scan rate of $500mVs^{-1}$. It has been reported that square wave voltammogram can be obtained in just a few seconds as compared to the pulse techniques which takes about 3 min (Borman 1982). But it cannot be denied that pulse techniques offer low instrumentation cost with easy applicability and availability. Differential Pulse Polarography/Differential Pulse Voltammetry is often a choice for drug analysis as it can give limit of detection as low as 10^{-8} M (Gupta et al. 2011). This technique has been used extensively for the trace determination of electroactive compound in pharmaceuticals (Kilic et al. 2006; Nigovic and Simunic, 2003; Radi et al. 2005; Shahrokhian et al. 2005; Radi and Elmogy, 2005; Jain et al. 2010; Belgaied and Trabelsi, 2002; Adhoum and Monser, 2005; Fiorucci and Cavalheiro, 2002) and biological fluids (Farhadi and Karimpour, 2007). Stripping analysis is the foremost known technique for trace analysis which includes a pre-concentration step (Wang 1988; Hart 1990; Kissinger and Heineman, 1996; Smyth and Vas, 1992). The stripping analysis offers the following advantages of low detection limit, low determination limit, high sensitivity, wide spectrum of analytes, simplicity, low cost and least interference from the matrix (Gratteri et al.1992; Wang et al. 1999; Farghaly et al. 2000).

Importance of Pharmaceutical Drug Analysis

Since the past decades, a rapid development of pharmaceutical compounds has made an accelerated growth. Medicinal chemists, pharmacologists, biochemists, analytical chemists and medical professionals have leaded the way with an ultimate objective to combat human diseases. In this effort, the chemical purity of the drug in all its forms is extremely crucial and vital. Thus, synthesis and characterization of such molecules and their analysis becomes important to create preliminary safety and therapeutic efficacy data which helps in further investigations. With the advent of Computer-Aided-Drug Modelling (CADM), new drug entities have paved a way towards more specific, potent, and above all lesser toxic drugs to improve the ultimate quality of human life. Keeping this in view, a viable, rigorous, accurate and precise analytical method must be evolved with the passage of time (Valagaleti et al. 2003; Kar, 2005).

A detailed literature survey about the pharmaceutical drugs being analyzed voltammetrically with different types of chemically modified electrodes along with their limit of detection has been concisely presented in the table 1.

Table 1: List of some pharmaceutical drugs studied electrochemically using nanocomposite modified sensors as reported in the literature

Name of Drug	Working electrode	Method	LOD/LOQ	Reference
Pyridoxine HCl	mCPE	DPV	0.4l gm/L	Desai et al. 2008
Loracarbef	GCE	AdSV	$6x10^{-6}$ to $2x10^{-4}$ M	Topal et al. 2009
Captopril	mCPE	SWV	9.1×10^{-8} M	Maleh et al. 2010
Sulfasalazine	MIP/CPE	DPV	4.6×10^{-9}mol/L	Sadeghi et al. 2012
Tranexamic acid	GR/Bi_2O_3/GCE	CV & SWV	15.05 µg/ml	Shrivastava et al. 2012
Acebutolol	HMDE	SWAdSV	5×10^{-7} M	Al-Ghamdi et al. 2012
Lamotrigine	Pyrolytic graphite electrode	CV	80 nM	Saberi and Shahrokhian, 2012
Glucose	Nafion/PtPd-MWCNTs/GCE	CV	0.031 mM	Chen et al. 2012
Acyclovir	Thin film Mercury electrode	AdSV	1.0×10^{-9} mol/L	Castro et al. 2013
Albendazole	BDDE	DPV	0.0625 µmol/L	Laurencao et al. 2013
Famotidine	Graphite electrode GE	CV & DPV	$3.73x10^{-7}$ mol/L	Yagmur et al. 2014
Methotrexate	MWCNT/GCE	DPAdSV	$3.3x10^{-8}$ mol/L	Oliviera et al. 2013
Ketoconazole	Cyclo-dextrin/GCE	CV, DPV	10.14×10^{-8} M	El-Ries et al. 2013
Simvastatin	p-tol/sulfonic acid/GCE	CV	$1.5 X10^{-7}$ M	Deepal et al. 2013
Norepinephrine	MWCNT/IL/CPE	CV, SWV, CA	0.08 µmol/ L	Ansari et al. 2013
Enalapril	MWCNT/CPE	SWV	0.81 µmol/L	Valezi et al. 2014
Ondansetron	MWCNTs-Nafion/GCE	AdSV	3.1×10^{-8} M	Nigović et al. 2014
Entecavir	GCE	SWCAdSV	$2.27x10^{-6}$ mol/L	Jhankal et al. 2015
Paracetamol	GCE	CV and DPV	$3.69x10^{-7}$ mol/L	Engin et al. 2015
Omeprazole	Pyrolytic graphite electrode	AdSV	3 nM	Shahrokhian et al. 2015
Metformin	Pyrogallol/CPE	CV and DPV	6.63×10^{-8}mol/L	Attia et al. 2015
Methyldopa	Fe:Co nano-alloy (Fe:Co/NL/CPE)	SWV	0.03 µM	Gupta et al. 2015
Etoposide	Sepiolite/CPE	AdsSWV	0.00262µmol/L	Bayraktepe et al. 2015
Amantadine	mGCE	DPV	15 ng/ml	Dominguez and Hernandez, 2015
Dropropizine	CPE	DPAV	0.046 ug/ml	Zayed and Arida, 2015
Dopamine	AuPt/GR/CPE	DPV	0.1 µM	Zhao et al. 2015

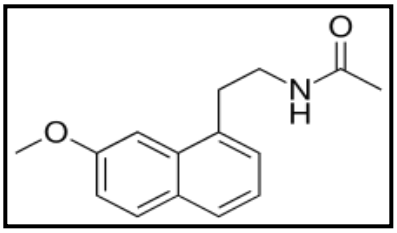
OBJECTIVES

The present piece of work is proposed taking some commonly used pharmaceutical compounds like **Agomelatine, Balofloxacin, Itopride and Ranolazine** aiming to fulfill the following objectives:

- Synthesis of the nanocomposites comprising metal oxide-carbon nanomaterial (graphene, g-C_3N_4, CNTs).
- Characterization of the prepared nanocomposites using techniques such as FTIR, SEM, XRD, AFM and UV-VIS spectrophotometry.
- Electrode fabrication with the synthesized nanocomposites.
- Electrochemical characterization of the modified electrode using cyclic voltammetry and electrochemical impedance spectroscopy (EIS).
- Study of voltammetric behavior and reaction mechanisms of Agomelatin, Balofloxacine, Itopride and Ranolazine.
- Standardization of the optimum conditions with special reference to effect of pH, Potential and scan rate, nature of surfactants and drug stability using Cyclic, square-wave and differential pulse voltammetric techniques.
- Validation of the methods in terms of sensitivity, limit of detection, limit of quantification, accuracy, precision and specificity.

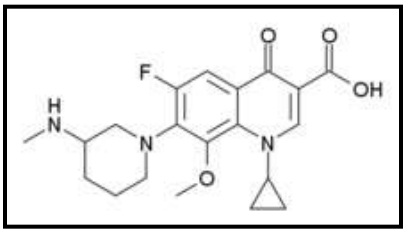
PHARMACEUTICAL DRUGS UNDER STUDY

- ***AGOMELATINE***



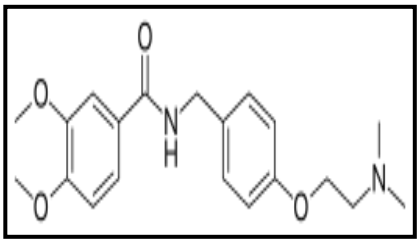
- **IUPAC**-*N*-[2-(7-methoxynaphthalen-1-yl)ethyl]acetamide
- Melatonergic Anti-Depressant drug
- Therapeutic benefits in circadian rhythm disorders (Taylor, et al. 2014).
- Sold under trade name: Agopose, Agoprex, Agoviz, Agotine, Simelatin, etc.

- ***BALOFLOXACIN***



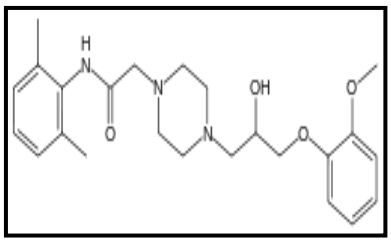
- **IUPAC**-1-Cyclopropyl-6-fluoro-8-methoxy-7-(3-methylaminopiperidin-1-yl)-4-oxoquinoline-3- carboxylic acid.
- Fluoroquinolone Anti-biotic (Alksne 2003)
- Treatment- uncomplicated urinary tract infections, infective ophthalmitis, community-acquired pneumonia, acute exacerbation, sinusitis, skin infections and chronic bronchitis.
- Sold under trade name: B-Cin, Baloforce, Bazucin, Balomac, Balista, etc.

- ***ITOPRIDE***



- **IUPAC**- N-{4-[2-(dimethylamino)ethoxy]benzyl}-3,4-dimethoxybenzamide.
- Inhibits dopamine and have a gastrokinetic effect.
- Treatment - functional dyspepsia and other gastrointestinal conditions (Holtmann et al. 2006)
- Sold under trade name: Ganaton, Motiza, Itomis, Itza etc.

- ***RANOLAZINE***



- IUPAC-(*RS*)-*N*-(2,6-Dimethylphenyl)-2-[4-[2-hydroxy-3-(2-methoxyphenoxy)-propyl]piperazin-1-yl]acetamide.
- Anti-Anginal Drug (Banon et al. 2014)
- treat chronic angina (ongoing chest pain or pressure that is felt when the heart does not get enough oxygen)
- Sold under trade name: Ranozax, Rancad, Raux, Caroza, Cartinex etc.

CRITERIA FOR SELECTION OF PHARMACEUTICAL DRUGS

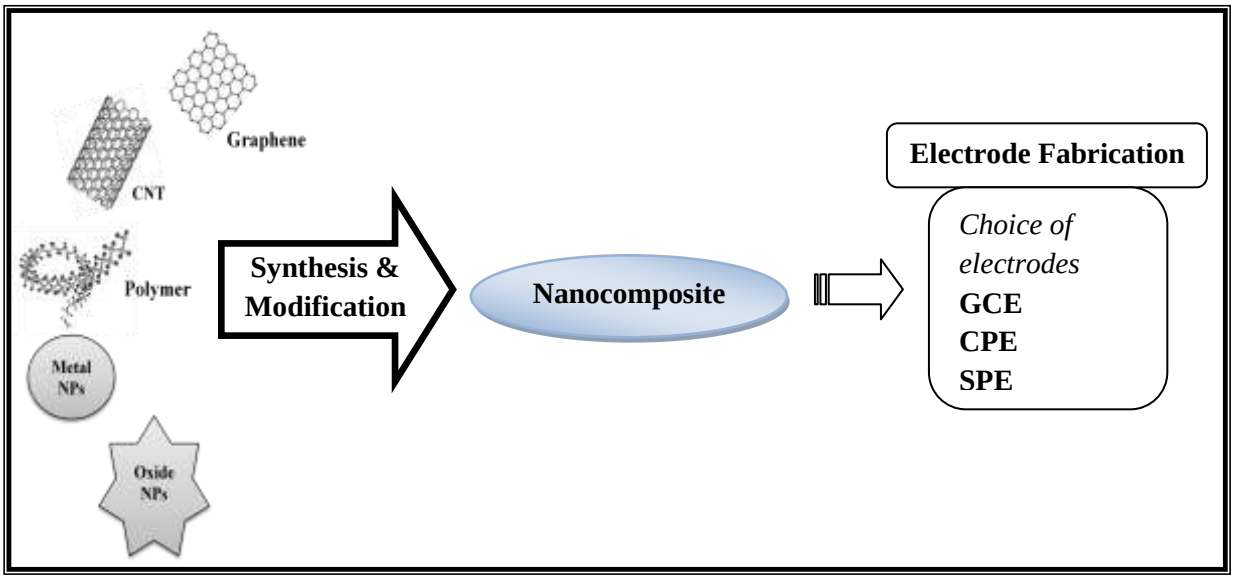
- A detailed survey of literature revealed that the chosen drugs have not been explored voltammetrically yet.
- The pharmaceutical drugs selected offer important therapeutic properties.
- The drugs were found to be electroactive in nature which is an important criterion for electrochemical analysis.

METHODOLOGY

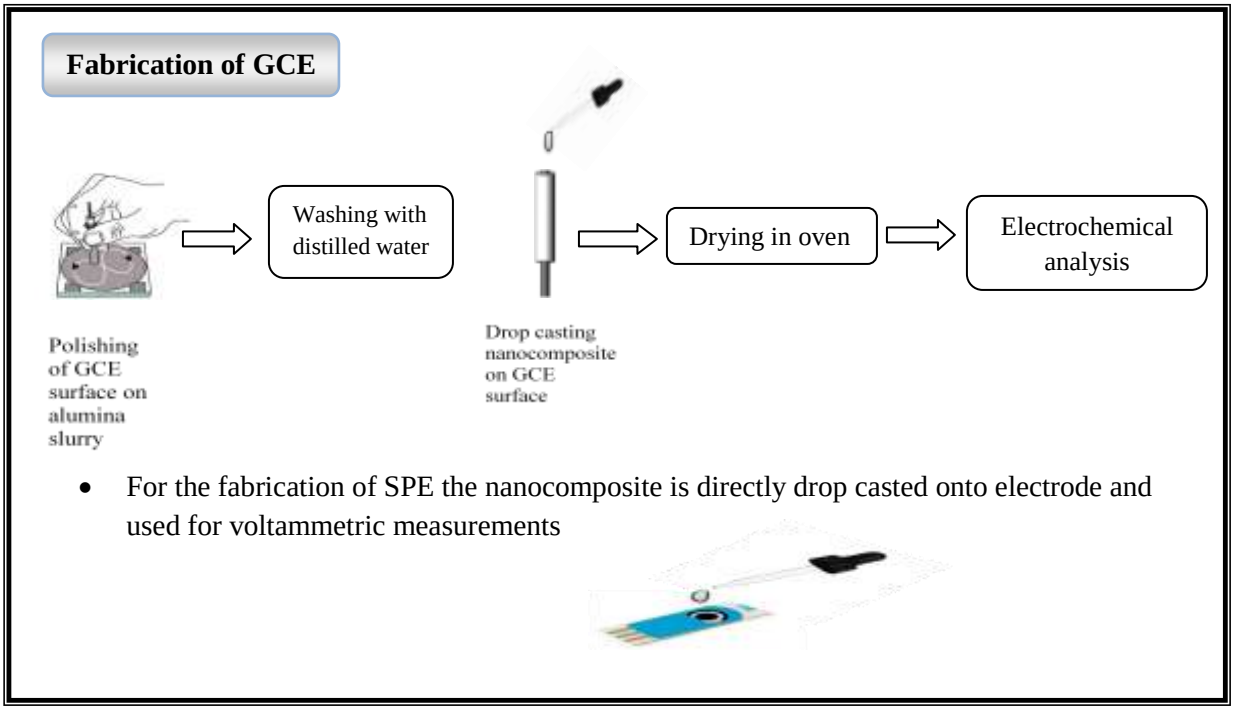
Plan of work

The proposed research work will be carried out using Standard protocols and procedures as reported in the literature. The plan of the present work is displayed schematically as shown:

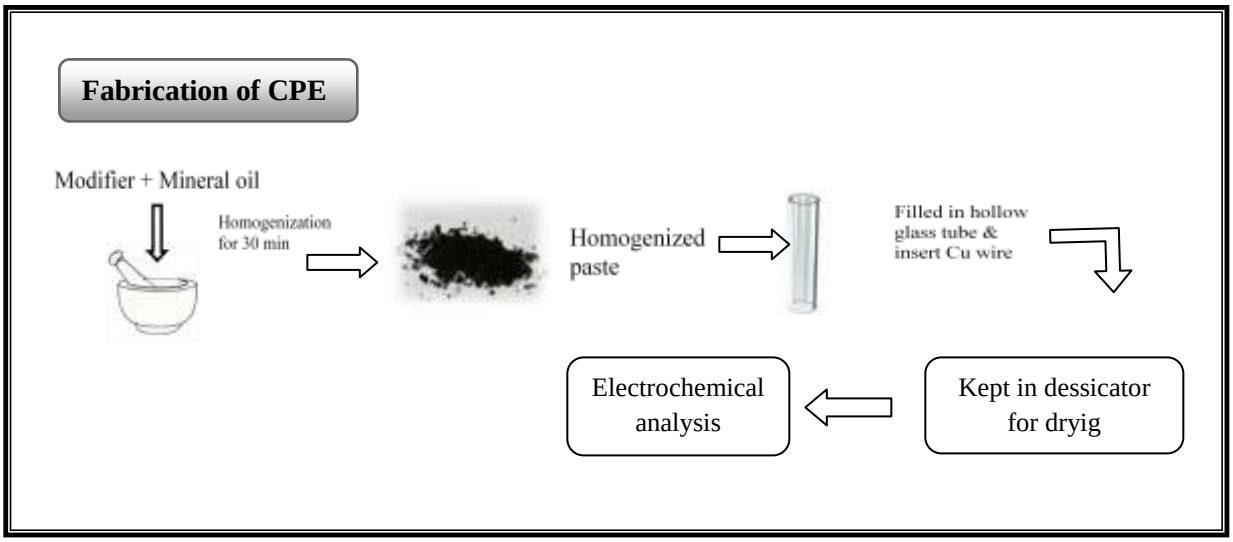
(A) Preparation of Nanocomposites for Chemical modifications of the electrode.



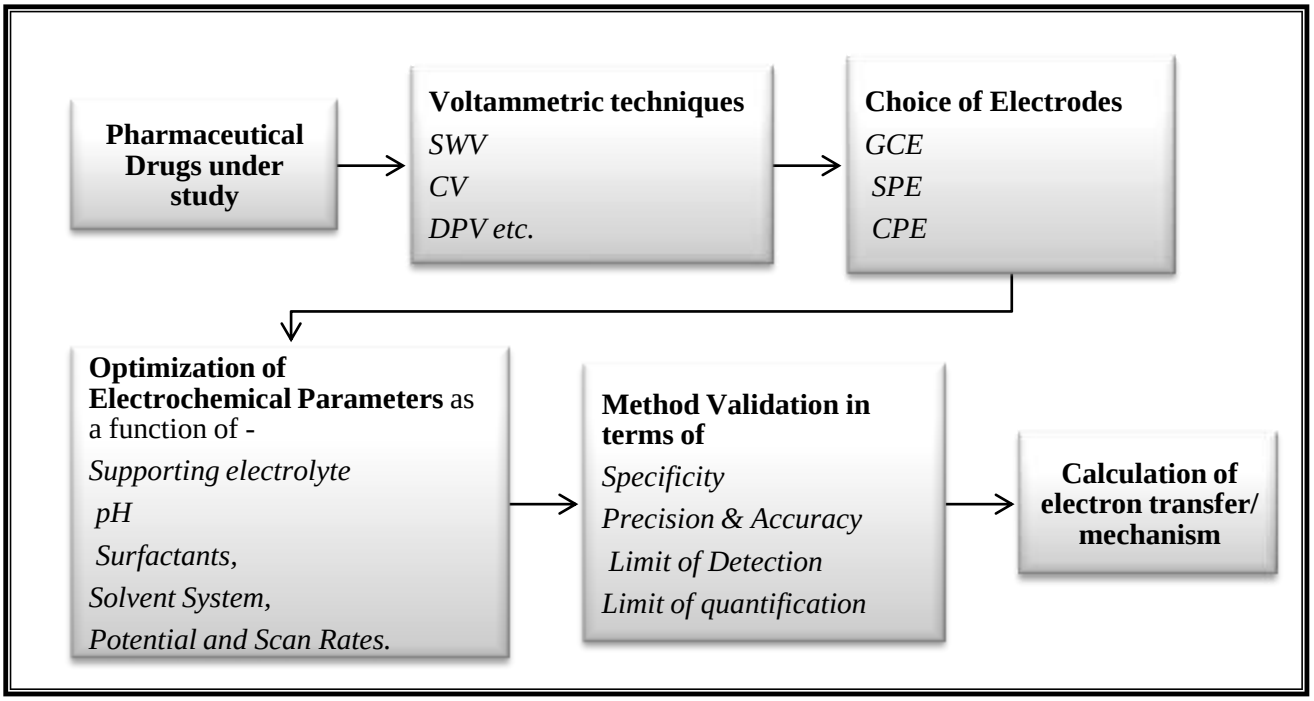
(B)Fabrication of electrodes


Fabrication of GCE
Washing with distilled water
Drying in oven
Electrochemical analysis
Polishing of GCE surface on alumina slurry
Drop casting nanocomposite on GCE surface

- For the fabrication of SPE the nanocomposite is directly drop casted onto electrode and used for voltammetric measurements


Fabrication of CPE
Modifier + Mineral oil
Homogenization for 30 min
Homogenized paste
Filled in hollow glass tube & insert Cu wire
Kept in dessicator for dryig
Electrochemical analysis

(C) Standardization and optimization of electrochemical parameters for the evaluation of electrocatalytic response of pharmaceutical drugs under study.

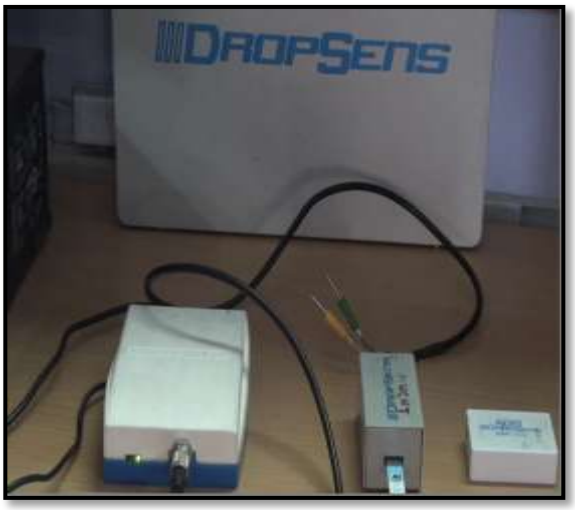


INSTRUMENTATION

AUTOLAB PGSTAT 302N:

- Autolab PGSTAT 302N is purchased from Metrohm Utrecht Netherlands.
- Autolab with its user interface NOVA (version 1.11) is a boon in all the electrochemical voltammetric studies.

DROPSENS µSTAT 400:



- µSTAT400 can be used with one or two electrode systems and can be applied for voltammetric, Amperometric or Potentiometric measurements. It is powered with Li-ion battery and can be connected easily to a PC via USB.
- The use of Screen Printed Modified electrodes is the forte of the instrument. It is a Portable instrument.

SIGNIFICANCE OF THE PROPOSED WORK

- ☑ **Quality control:** At every stage of development of pharmaceutical compounds, it needs to be monitored for its purity. This requires a simple, fast, sensitive and accurate method for the analysis of pharmaceutically active compound.
- ☑ **Cost effectiveness:** Low running cost and cheaper instrumentation, simplicity of instrumentation, higher sensitivity and selectivity for trace determination of analyte and evaluation of structure-activity relationship forms the forte of the electrochemical studies.
- ☑ **Chemically Modified Electrodes:** Modification at the surface of electrode is an emerging trend which results in enhanced sensitivity and selectivity of the analyte in the solution system with low limits of detection.
- ☑ **Drug Formulations:** Electroanalytical techniques help to understand the redox properties of pharmaceutically active compounds which can lead to development and growth in the field of pharmacology.

REFERENCES

Abdine, H.; Belal, F. *Talanta* 2002, 56, 97–104.

Acuna, J. A.; Fuente, C. D. L.; Vazquez, M. D.; Tascon, M. L.; Gomez, M. I.; Mata, F.; Batanero, P. S. E. *J. Pharm. Biomed. Anal*. 2002, 29, 617–622.

Adhoum, N.; Monser, L. *J. Pharm. Biomed. Anal.* 2005, 38, 619–623.

Al-Ghamdi, A. F.; Hefnawy, M. M.; Al-Majed, A.; Belal, F. F. *Chem. Cent. J.* 2012, 6, 1-8.

Alksne, L. *Curr Opin Investig Drugs* 2003, 4, 224–9.

Ames, J. R. *J. Pharm. Sci.* 1991, 80, 293-295.

Ansari, M.; Kazemi, S.; Khalilzadeh, M. A.; Maleh, K. H.; Zanousi, M. B. P. *Int. J. Electrochem. Sci*. 2013, 8, 1938 -1948.

Attia, A. K.; Salem, W. M.; Mohamed, M. A. *Acta Chim. Slov*. 2015, 62, 588–594.

Banon, D.; Filion, K. B.; Budlovsky, T.; Franck, C.; Eisenberg, M.J. *Am J Cardiol.* 2014, 113, 1075-82.

Bayraktepe, D. E.; Yanardağ, T.; Yazan, Z.; Aksüt, A. *Rev. Roum. Chim.*, 2015, 60, 287-295.

Belgaied, J. E.; Trabelsi, H. *J. Pharm. Biomed. Anal.* 2002, 30, 1417–1423.

Borman, S. *Anal. Chem.*1982, 54, 698A-705A.

Bozal, B.; Uslu, B.; Ozkan, S. A. A review of electroanalytical techniques for determination of Anti-HIV drugs, *Int. J. Elec.* 2011, doi:10.4061/ 2011/ 343947.

Cao, X.; Wang, N.; Jia, S.; Shao, Y. *Anal. Chem.* 2013, 85, 5040-5046.

Castro, A. A.; Cordoves, A. I. P.; Farias, P. A. M. *Anal. Chem. Insights* 2013, 8, 21–28.

Chen, K.J.; Lee, C.F.; Rick, J.; Wang, S. H., Liu, C. C.; Hwang, B. J. *Biosensors And Bioelectronics* 2012, 33, 75–81.

Dakova, B.; Kauffmann, J.M.; Evers, M.; Lamberts, L.; Patriarche, G. J. *Electrochim. Acta*, 1990, 35, 1133-1138.

Deepal, M. B.; Mamatha, G. P.; Arthoba, Y.; Naik; Sherigara, B. S. *Int. J. Pharm. Chem*. 2013, 3, 9-16.

Desai, P. B.; Kotkar, R. M.; Srivastava, A. K. *J.Solid State Electrochem.* 2008, 12, 1067–1075.

Domínguez , C. S. H.; Hernández, P. *Am. J. Anal. Chem.* 2015, 6, 623-630.

Donten, M.; Stojek, Z. in *Nanoparticles and Nanostructured Materials Used in Modification of Electrode Surfaces;* ACS Symposium Series, American chemical Society: Washington DC, 2012.

El Ries, M. A.; Ghany, M. F. A.; Hussin, L. A.; El-Anwar, F. M.; Mohamed, M. A. *Bull. Fac. Pharm. (Cairo Univ.)* 2013, 51, 49–55.

Ellis, G. P.; West, G. B. in *Progress in Medicinal Chemistry*; North-Holland: Amsterdam, 1975.

Engin, C.; Yilmaz, S.; Saglikoglu, G.; Yagmur, S.; Sadikoglu, M. *Int. J. Electrochem. Sci.* 2015, 10, 1916-1925.

Farghaly, O. A.; Abdel Hameed, R. S.; Abu- Nawwas, A. H. *Int. J. Electrochem. Sci.*, 2014, 9, 3287-3318.

Farghaly, O. A. E. M. *J. Pharm. Biomed. Anal*, 2000, 23, 783–791.

Farhadi, K.; Karimpour, A. *J.Chin. Chem.Soc.* 2007, 54, 165–172.

Fiorucci, A. R.; Cavalheiro, E. T. G. *J. Pharm. Biomed. Anal.* 2002, 28, 909–915.

Gao, Y. S.; Xu, J. K.; Lu, L. M.; Wu, L. P.; Zhang, K. X.; Nie, T.; Xhu, X. F.; Wu, Y. *Biosens. Bioelectron.* 2014, 139, 3991-3998.

Gratteri, P.; Pinzauti, S.; Papeschi, G.; La Porta, E.; Furlenetto, S. *Farmaco*, 1992, 47, 695–709.

Guan, C. L.; Ouyang, J.; Li, Q. L.; Liu, B. H.; Baeyens, W. R.G. *Talanta* 2000, 50, 1197-1203.

Guo, W.; Lin, H.; Liu, L.; Song, J. *J. Pharm. Biomed. Anal.* 2004, 34, 1137–1144.

Gupta, V. K.; Khosravi, Saleh, K. H.; Alizadeh, M.; Sharafi, S. *Int. J. Electrochem. Sci.* 2015, 10, 3269 – 3281.

Gupta, V. K.; Jain, R.; Radhapyari, K.; Jadon, N.; Agarwal, S. *Anal. Biochem.* 2011, 408, 179–196.

Hart, J.P. in *Electroanalysis of Biological Important Compound*; Ellis Horvood Limited: New York, SA, 1990.

Heyrovsky, J. *Chem. List*, 1922, 16, 259.

Holtmann, G.; Talley, N. J.; Liebregts, T.; Adam, B.; Parow, C. N. *Engl. J. Med.* 2006, 354, 832–840.

Innis, P.; Wallace, G. J. *Nanosci. Nanotech.* 2002, 2, 441-451.

Jain, A. K.; Gupta, V. K.; Radi, S.; Singh, L. P.; Raisoni, J. R. *Electrochim. Acta* 2006, 51, 2547–2553.

Jain, A. K.; Gupta, V. K.; Singh, L. P.; Khurana, U. *Analyst*, 1997, 122, 583–586.

Jain, R.; Gupta, V. K.; Jadon, N.; Radhapyari, K. *Anal. Biochem.* 2010, 407, 79–88.

Jhankal, K. K.; Sharma, A.; Ramswaroop, Sharma, D. K. *J. Pharm. Sci. & Res.* 2015, 1, 10-13.

Kang,T. F.; Shen, G. L.; Yu, R. Q. *Anal. Chim. Acta* 1997, 354, 343-349.

Kar, A. in *Pharmaceutical Drug Analysis*; New age international (P) Ltd., Publishers: New Delhi, India, 2005.

Kauffmann, J.M.; Vire, J. C. *Anal. Chim. Acta* 1993,273, 329-334.

Kauffmann, J.M.; Vire, J.C.; Patnarche, G. J.; Hememan, W. H. *Analyst* 1985, 110, 349.

Kilic,C. S. E.; Uslu, B.; Dogan, B.; Ozgen, U.; Coskun, M. *J. Anal. Chem.* 2006, 61, 1113–1120.

Kissinger, P.T.; Heineman, W.R. in *Laboratory Techniques in Electroanalytical Chemistry 2nd ed*; Marcel Dekker: New York, USA, 1996.

Kounaves, S. P. in *Handbook of Instrumental Techniques for Analytical Chemistry*; Prentice Hall: New York, NY, 1997.

Kovacic, P.; Ames, J. R.; Rector, D. L.; Jawdosmk, M.; Ryan, M. D. *Free Rad. Bioi Med.* 1989, 6, 131.

Laurencao, B. C.; Baccarin, M.; Medeiros, R. A.; Filho, R. R. C.; Filho, F. O. *J. Electroanal. Chem.* 2013, 15–19.

Li, J.; Yang, J.; Yang, Z.; Li, Y.; Yu, S.; Xua, Q.; Hu, X. *Anal. Methods* 2012, 4, 1725-1728.

Luo, X.; Morrin, A.; Killard, A. J.; Smyth, M. R. *Electroanalysis* 2006, 18, 319 – 326.

Maleh, K. H.; Ensafi, A.A.; Allafchian, A.R. *J.Solid State Electrochem.* 2010, 14, 9-15.

Mars, D. R. D.; Shain, I. *Anal. Chem*. 1957, 29, 1825-1827.

Nickelby, J. G.; Kooke, W. D. *Anal. Chem*. 1957, 29, 933.

Nigović, B.; Mornar, A.; Sertić, M. *Microchim. Acta*, 2016, 1-9.

Nigović, B.; Sadiković, M.; Sertić, M. *Talanta* 2014, 122, 187-94.

Nigovic, B.; Simunic, B. *J. Pharm. Biomed. Anal.* 2003, 32, 197–202.

Okpala, C. C. *Int. j. adv. engg. tech.* 2014, 5, 12-18.

Oliveira, G. G.; Janegitz, B. C.; Zucolotto, V.;Filho, F. O. J. F. *CEJC*, 2013, 11, 1837-1843.

Ozkan, S. A.; Uslu, B.; Enein, H. Y. A. *Crit. Rev. Anal. Chem.* 2003, 33, 155-181.

Patriarche, G. J.; Zhang, H. *Electroanalysis* 1990, 2, 573-579.

Plambeck, J. A. in *Electroanalytical Chemistry, Basic Principles and Application;* Wiley Interscience: USA, 1982.

Radi, A.; Elmogy, T. *Farmaco*, 2005, 60, 43–46.

Radi, A.*;* El-Shahawi, M. S.*;* Elmogy, T. *J. Pharm. Biomed. Anal.* 2005, 37, 195–199.

Raj, C. R.; Okajima, T.; Ohsaka, T. J. *Electroanal. Chem*. 2003, 543, 127-133.

Rick, J.; Tsai, M. S.; Hwang, B. J. *Nanomaterials* 2016, 6, 5.

Saberi, R.S.; Shahrokhian, S. Bioelectrochemistry 2012, 84, 38-43.

Sadeghi; Motaharian, S.; Moghaddam, A.; Zeraatkar, A. *Sens. and Actuators, B* 2012, 168, 336–344.

Santos, A. L.; Takeuchi, R. M.; Mariotti, M. P.; De Oliveira, M. F.; Zanoni, M. V. B.; Stradiotto, N. R. *Farmaco*, 2005, 60, 671–674.

Sarre, S.; Michotte, Y.; Herregodts, P.; Deleu, D.; Klippel, N. D.; Ebinger, G. *J.Chromatogr*. 1992, 575, 207-212.

Shahrokhian, S.; Karimi, M.; Khajehsharifi, H. *Sens. Actuators B* 2005, l109, 278–284.

Shahrokhian, S.; Masoumeh; Ghalkhani; Bayat, M.; Bidkorbeh, G. F. *Iran J. Pharm. Res.* 2015 14, 465–471.

Shrivastava, R.; Sharma, R.; Satsangee, S. P.; Jain, R. *J. Electrochem. Soc.* 2012, 159, 795-800.

Siddiqui, M. R.; Alothman, Z. A.; Rahman, A. Analytical Techniques in Pharmaceutical analysis: A review, *Arabian Journal of Chemistry*, 2013, http://dx.doi.org/10.1016/j.arabjc.2013.04.016.

Silva, M. L. S.; Garcia, M. B. Q.; Lima, J. L. F. C.; *Anal. Chim. Acta* 2006, 573, 383–390.

Smyth, M. R.; Vos, G. J. in *Analytical Voltammetry;* Elsevier Science: Amsterdam, Netherlands, 1992.

Stradiotto, N.R.; Yamanaka, H.; Zanoni, M.V.B. *J. Braz. Chem. Soc*. 2003, 14, 159-173.

Sun, D.; Zhang, H. *Microchim. Acta* 2007, 158, 131–136.

Tapsoba, J. E.; Belgaied, K.; Boujlel; *J. Pharm. Biomed. Anal.* 2005, 38, 162–165.

Taylor, D.; Sparshatt, A.; Varma, S.; Olofinjana, O. *B.M.J.* 2014, 348, g1888.

Topal, B. D.; Ozkan, S. A.; Uslu, B. *TOCBMJ*, 2010, 3, 56-73.

Topal, B. D.; Golcu, A.; Ozkan, S. A. *Anal. Lett.* 2009, 42, 689–705.

Torres, R. F.; Mochon, M. C.; Sanchez, J. C. J.; Lopez, M. A. B.; Perez, A. G. *J. Pharm. Biomed. Anal.* 2002, 30, 1215–1219.

Uslu, B.; Demircigil, B. T.; Ozkan, S. A.; Senturk, Z.; Aboul-Enein, H. Y. *Pharmazie*, 2001, 56, 938–941.

Valagaleti, R.; Burns, P.K.; Michael, G. *Drug Inf. J.* 2003, 37, 407-438.

Valezi, C. F.; Duarte, E. H.; Mansano, G. R.; Antonia, L. H. D.; Tarley, C. R. T.; Sartori, E. R. *Sens. Actuators, B* 2014, 205, 234–243.

Wang, J. in *Electroanalytical Techniques in Clinical Chemistry and Laboratory Medicine*; VCH: New York,USA, 1988.

Wang, J.; Tian, B.; Wang, J.; Lu, J.; Olsen, C.; Yarnitzky, C.; Olsen, K.; Hammerstrom, D.; Bennet, B. *Anal. Chim. Acta* 1999, 385, 429–435.

Wang, Y.; Xu, H.; Zhang, J.; Li, G. *Sensors* 2008, 8, 2043-2081.

Xu, J. Z.; Zhu, J. J.; Wang, H.; Chen, H. Y. *Anal. Lett*. 2003, 36, 2723-2733.

Yagmur, S.; Yilmaz, S.; Saglikoglu, G.; Uslu, B.; Sadikoglu, M.; Ozkan, S. A. *J. Serb. Chem. Soc*. 2014, 79, 53–62.

Zhang, X.; Ju, H.; Wang, J.in *Electrochemical sensors, biosensors and their biomedical applications*; Elsevier: Academic press, 2008.

Zhao, Z.; Zhang, M.; Chen, X.; Li, Y.; Wang, J. *Sensors* 2015, 15, 16614-16631.

Zhou X.; Wang, F.; Zhu, Y.; Liu, Z. *J. Mater. Chem*. 2011, 21, 3353-3358.

Zhu, C.; Yang, G., Li, H.; Du, D.; Lin, Y. *Anal. Chem*, 2015, 87, 230-249.